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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/012,904	01/23/98	MEADE	[illegible]

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EXAMINER	
KERR, J	

ART UNIT	PAPER NUMBER
1635	8

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/012,904	Meade et al.
Examiner	**Group Art Unit**
Janet M. Kerr	1633

☒ Responsive to communication(s) filed on *Jul 27, 1999* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *19-25* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *19-25* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3 and 5*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Applicants' amendment, filed on 7/27/99, has been entered.

Applicant's election of Group II, claims 19-25, in Paper No. 7 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-18 have been canceled.

Claims 19-25 are being examined on the merits.

Specification

The disclosure is objected to because of the following informalities: Applicants are required to update the priority data to indicate that Application Serial No. 08/170,579, is now U.S. Patent No. 5,827,690.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19 and 21-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for generating a construct comprising a tissue-specific promoter operably linked to a sequence encoding an immunoglobulin, does not reasonably provide enablement for using the sequence to generate any transgenic mammal harboring the construct. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are directed to a DNA construct comprising a promoter and sequence encoding an immunoglobulin, wherein the promoter directs expression of the construct in mammary gland epithelial cells of transgenic mammals harboring the DNA construct, and wherein the immunoglobulin is secreted into the milk of the transgenic mammal in an assembled form.

While the specification is enabling for a DNA construct comprising a mammary tissue-specific promoter and sequences encoding heavy and light chains of immunoglobulins, the specification is non-enabling for the expression and secretion of an assembled immunoglobulin into the milk of all transgenic mammals *per se*.

The intended use of the DNA construct is to generate transgenic mammals which express the transgene in mammary gland epithelial cells such that the immunoglobulins are secreted, in an assembled form, into the milk of a lactating transgenic mammal. The generation of constructs comprising "mammary tissue-specific" promoters, such as the casein, lactoglobulin, lactalbumin, and whey acid protein promoters, to direct expression of a sequence encoding a foreign protein into the milk of transgenic mammals such as cows, goats, sheep, and mice is well known in the art (see, e.g., Table 6 in Houdebine, Journal of Biotechnology, 34:269-287). However, the state of the art at the time of filing is such that generation of transgenic mammals other than mice, via embryonic stem cell technology, is neither routine nor predictable. For example, Bradley *et al.* state that the key requirement in any experiment involving the generation of a specific modification in ES cells is that the clone should retain all of its potential to contribute to both the somatic lineages and the germ line following microinjection of the cells into blastocyst-stage embryos (see pages 535-536, bridg. sentence in Bradley *et al.*, Bio/Technology, 10:534-539, 1992). Bradley *et al.* disclose that at that time, there were no ES cells for any animal other than a mouse which had been established to give rise to somatic tissues or germ cells *in vivo*. Similarly, Seamark (Reproductive Fertility and Development, 6:653-657, 1994) discloses that totipotency for ES cell technology in many livestock species has not been demonstrated (see, e.g., Abstract). Moreover, Mullins *et al.* teach that while chimeric animals for several species has been produced using purported ES cells, germ line transmission of an ES cell has not been demonstrated in species other than mice. In addition, Mullins *et al.* disclose that "The use of nonmurine species

for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another" (see page S37-S38, bridg. sentence, page S38, col. 1, lines 23-26, and page S39, under "Summary" in Mullins *et al.*, J. Clin. Invest., 98:S37-S40, 1996). In view of the state of the art at the time of filing, the generation of a transgenic mammal from any species, which is an essential element for the implementation of the claims, was not readily available to the skilled artisan either through the art or by disclosure in the specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 19-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is rendered vague and indefinite by the phrase "heterologous immunoglobulin protein-coding sequence" as it is unclear if the sequence is heterologous to the promoter sequence, to the transgenic mammal, or both.

Claim 19 is further rendered vague and indefinite by the phrase "preferential expression" as it is unclear if the expression of the protein is tissue-restricted, tissue-specific, expressed during a certain time of development, expressed under certain physiological conditions, etc. Thus, the metes and bounds of the phrase are unclear.

Claim 19 is also confusing by the functional language utilized in describing the construct. For example, while promoters are known to "direct" expression of a gene, and while constructs can be expressed in mammary gland epithelial cells in a mammal harboring the construct such that a foreign protein can be secreted into the milk of the transgenic animal, it is unclear how a promoter, per se, can "result in" preferential expression of the protein-coding sequence or "thereby provide" a heterologous and assembled immunoglobulin in the milk of a transgenic

animal. Moreover, in light of the specification which describes two distinct DNA constructs which separately encode a heavy chain or a light chain, the claim is confusing because it recites "A DNA construct comprising a heterologous immunoglobulin protein-coding sequence" which when expressed, is assembled. It is unclear what protein-coding sequence is required such that expression of the sequence results in an assembled immunoglobulin in the milk. Thus, the metes and bounds of what elements are required in the heterologous immunoglobulin protein-coding sequence such that the immunoglobulin is secreted into milk in an assembled form, are unclear.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 19-21, 24, and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Meade *et al.* (U.S. Patent No. 4,873,316, 1989).

Meade *et al.* disclose a DNA construct for production of recombinant proteins comprising a milk-specific protein promoter or any promoter sequence specifically activated in mammary tissue, operatively linked to a DNA sequence coding for a desired recombinant protein through a DNA sequence coding for a signal peptide that permits the secretion and maturation of the desired recombinant protein in the mammary tissue. The construct can be transgenically incorporated into mammalian embryos obtained from cows, sheep, goats, mice, and pigs, for example, such that the recombinant protein product is subsequently expressed and secreted into or along with the milk of the lactating transgenic animal (see, e.g., column 2, lines 41-68). The milk-specific protein

promoter or promoter sequence specifically activated in mammary tissue can be selected from the casein promoters, β-lactoglobulin promoter, or the long terminal repeat promoter of the mouse mammary tumor virus (see, e.g., column 3, lines 1-15). The DNA sequence coding for a desired recombinant protein can include sequences encoding immunoglobulins (see, e.g., column 3, lines 30-40).

Thus, DNA constructs comprising a promoter sequence operatively linked to a sequence encoding immunoglobulins, wherein the promoter preferentially expresses the immunoglobulins in the mammary gland epithelial cells of transgenic mammals such as cows, sheep, goats, mice, and pigs, and is secreted into the milk of the mammal, are anticipated by Meade *et al.*

Claims 19-21, 24, and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Meade *et al.* (U.S. Patent No. 5,750,172, 1998, effective filing date, 6/23/87).

Meade *et al.* disclose a DNA construct for production of recombinant proteins comprising a milk-specific protein promoter or any promoter sequence specifically activated in mammary tissue, operatively linked to a DNA sequence coding for a desired recombinant protein through a DNA sequence coding for a signal peptide that permits the secretion and maturation of the desired recombinant protein in the mammary tissue. The construct can be transgenically incorporated into mammalian embryos obtained from cows, sheep, goats, mice, and pigs, for example, such that the recombinant protein product is subsequently expressed and secreted into or along with the milk of the lactating transgenic animal (see, e.g., column 2, lines 41-65). The milk-specific protein promoter or promoter sequence specifically activated in mammary tissue can be selected from the casein promoters, β-lactoglobulin promoter, or the long terminal repeat promoter of the mouse mammary tumor virus (see, e.g., column 2, line 66, through column 3, line 12). The DNA sequence coding for a desired recombinant protein can include sequences encoding immunoglobulins (see, e.g., column 3, lines 26-34).

Thus, DNA constructs comprising a promoter sequence operatively linked to a sequence encoding immunoglobulins, wherein the promoter preferentially expresses the immunoglobulins in

the mammary epithelial cells of a transgenic animal and is secreted into the milk of the mammal, are anticipated by Meade *et al.*

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 19-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meade *et al.* (U.S. Patent No. 4,873,316, 1989), taken with Bischoff *et al.* (FEBS Letters, 305:265-268, 1992), Buhler *et al.* (Bio/Technology, 9:835-838, 1991), Gordon *et al.* (Bio/Technology, 5:1183-1187, 1987), Ebert *et al.* (Bio/Technology, 8:140-143, 1990, or Stinnakre *et al.* (FEBS Letters, 284:19-22, 1991), and further in view of Boss *et al.* (U.S. Patent No. 4,816,397, 3/28/89), Bruggemann *et al.* (WO 90/04036, 1990), and Weidle *et al.* (Gene, 98:185-191, 1991).

The claims are directed to a DNA construct comprising a heterologous immunoglobulin protein-coding sequence operatively linked to a promoter sequence that results in the expression of the protein-coding sequence in mammary gland epithelial cells to provide a heterologous and assembled immunoglobulin in milk.

Meade *et al.* disclose a DNA construct for production of recombinant proteins comprising a milk-specific protein promoter or any promoter sequence specifically activated in mammary tissue, operatively linked to a DNA sequence coding for a desired recombinant protein through a DNA sequence coding for a signal peptide that permits the secretion and maturation of the desired recombinant protein in the mammary tissue. The construct can be transgenically incorporated into mammalian embryos obtained from cows, sheep, goats, mice, and pigs, for example, such that the recombinant protein product is subsequently expressed and secreted into or along with the milk of the lactating transgenic animal (see, e.g., column 2, lines 41-68). The milk-specific protein promoter or promoter sequence specifically activated in mammary tissue can be selected from the casein promoters, β-lactoglobulin promoter, or the long terminal repeat promoter of the mouse mammary tumor virus (see, e.g., column 3, lines 1-15). The DNA sequence coding for a desired recombinant protein can include sequences encoding immunoglobulins (see, e.g., column 3, lines 30-40).

Meade *et al.* do not disclose that the promoter can be selected from whey acid protein promoter or the lactalbumin promoter, that the immunoglobulin comprises heavy and light chains, or that the immunoglobulin is of human origin.

With regard to the claim-designated promoter sequences, Bischoff *et al.* disclose a construct containing a sequence encoding a human α_1-antitrypsin variant operatively linked to 17.6 kb of the rabbit whey acid protein promoter, which results in expression and secretion of the α_1-antitrypsin variant into milk of a transgenic mouse (see, e.g., page 265, under "DNA construct", page 266, right column, first two paragraphs, and Table 1). Similarly, Gordon *et al.* disclose a DNA construct containing a sequence encoding human tissue plasminogen activator (t-PA) operatively linked to the promoter and upstream regulatory sequences from the murine whey acid protein gene, which results in expression and secretion of t-PA into milk of a transgenic mouse (see, e.g., pages 1183-1185, under the sections entitled "Construction of t-PA expression vector", and "Expression of biologically active t-PA in milk"). In addition, Ebert *et al.* disclose a DNA construct containing a sequence encoding human tissue plasminogen activator operatively linked to the mouse whey acid protein promoter which results in expression of the protein into

goat milk (see, e.g., page 835, right column, under "Generation of transgenic goats", page 836, Figure 1, and page 837, left column, under the section entitled "Expression of tPA in milk"). Moreover, Stinnakre *et al.* disclose a DNA construct comprising a sequence encoding ovine trophoblast interferon operatively lined to the promoter of the bovine α-lactalbumin gene, wherein the construct is capable of being expressed in the mammary gland of mice and secreted into milk (see, e.g., page 19, right column, under the section entitled "Establishment of the hybrid construct", page 20, under the section entitled "Expression of the transgene", and Figure 1, and page 21, Table 1). From the teachings of Bischoff *et al.*, Gordon *et al.*, Ebert *et al.*, or Stinnakre *et al.*, one of ordinary skill in the art would have had a high expectation of successfully producing a protein by the mammary gland which is secreted into the milk of a mammal using a DNA construct which contains a whey acid protein promoter or a lactalbumin promoter, which is known in the art to direct the expression of a foreign protein in the mammary gland.

With regard to a DNA sequence comprising a heterologous immunoglobulin protein-coding sequence, Boss *et al.* disclose DNA sequences encoding immunoglobulin heavy and light chains, which are capable of being expressed and assembled in transformed yeast cells (see, e.g., Figures 2 and 3, and column 22, line 1, through column 23, line 28). Bruggemann *et al.* disclose the expression of a recombinant chimeric immunoglobulin in body fluids, including milk, of transgenic mammals (see, e.g., pages 11-13, under Example 2, Table 1, and Figure 5). Bruggemann *et al.* indicate that transgenic animals can be used for specific antibody production thus allowing large scale production from milk, colostrum, sera, saliva, etc., as well as allowing the breeding of animals that yield a milk that is dosed with specific beneficial antibodies (see, e.g., page 12, last paragraph, bridging page 13). In addition, Weidle *et al.* disclose a construct comprising DNA sequences encoding immunoglobulin heavy and light chains, which are capable of being expressed in transgenic mice, rabbits and pigs harboring the construct (see, e.g., Figures 1 and 2, and pages 186-187 under "Synthesis of reconstituted Ab in the serum of transgenic mice, rabbits and pigs"). From the teachings of Boss *et al.*, Bruggemann *et al.*, and Weidle *et al.* one of ordinary skill in the art would have had a high expectation of successfully producing a construct

comprising a DNA sequence encoding a heterologous immunoglobulin sequence which can be expressed and assembled in a host cell or in the milk of a host mammal.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the DNA sequence disclosed by Meade *et al.* by substituting the casein promoters or β-lactoglobulin promoter, with promoter sequences obtained from the whey acid protein gene or α-lactalbumin gene in view of the teachings of Bischoff *et al.*, Gordon *et al.*, Ebert *et al.*, and Stinnakre *et al.* that these promoters direct expression of foreign proteins in mammary epithelial cells. It would also have been obvious to substituted the DNA sequence encoding the foreign protein, such as the immunoglobulin with the immunoglobulin sequences disclosed by Boss *et al.*, Bruggemann *et al.*, or Weidle *et al.* as hosts transformed with plasmids containing DNA sequences encoding immunoglobulins are capable of synthesizing and secreting the immunoglobulins. Taken together, one of ordinary skill in the art would have had a high expectation of successfully producing a heterologous and assembled immunoglobulin in the milk of a transgenic mammal which harbors a DNA sequence comprising the coding region of an immunoglobulin operatively linked to a promoter which directs expression of a foreign protein in mammary tissue.

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear, and convincing evidence to the contrary.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 19, 20, and 22-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, and 5 of U.S. Patent No. 5,750,172, May 12, 1998, effective filing date, June 23, 1987. Although the conflicting claims are not identical, they are not patentably distinct from each other because the expression system comprising a DNA sequence coding for a recombinant polypeptide chain operably linked to a casein promoter, wherein the recombinant polypeptide chain is selected from immunoglobulins, and wherein the expression system is utilized in generating a transgenic mammal which secretes a recombinant protein into the milk of the mammal, as claimed in U.S. Patent No. 5,750,172, contains the same DNA sequence components claimed in the instant application. Moreover, the intended use of the claimed DNA construct of the instant application, i.e., for the generation of a transgenic mammal which expresses the construct in mammary gland epithelial cells and secretes the immunoglobulin into the milk of the transgenic mammal, is encompassed in the patented claims.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirement of 37 CFR 1.821(d) as reference must be made to the sequences disclosed on pages 10 and 11 in the text of the description by use of the sequence identifier, preceded by "SEQ ID NO:".

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to Brian Stanton, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-2801. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633.

Janet M. Kerr, Ph.D.
Patent Examiner
Group 1600

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP ~~1800~~ 1630